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Maternal Exposure to Criteria Air Pollutants and Congenital Heart Defects in Offspring: Results from the National Birth Defects Prevention Study

Jeanette A. Stingone,[1] Thomas J. Luben,[2] Julie L. Daniels,[1] Montserrat Fuentes,[3] David B. Richardson,[1] Arthur S. Aylsworth,[4] Amy H. Herring,[5] Marlene Anderka,[6] Lorenzo Botto,[7] Adolfo Correa,[8] Suzanne M. Gilboa,[9] Peter H. Langlois,[10] Bridget Mosley,[11] Gary M. Shaw,[12] Csaba Siffel,[9] Andrew F. Olshan,[1] and the National Birth Defects Prevention Study

[1]Department of Epidemiology, Gillings School of Global Public Health University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [2]National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA; [3]Department of Statistics, North Carolina State University, Raleigh, North Carolina, USA; [4]Departments of Pediatrics and Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [5]Department of Biostatistics, Gillings School of Global Public Health University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [6]Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health Boston, Massachusetts, USA; [7]Department of Genetics and Pediatrics, University of Utah, Salt Lake City, Utah, USA; [8]Department of Pediatrics, University of Mississippi Medical Center, Jackson, Mississippi, USA; [9]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [10]Texas Center for Birth Defects Research and Prevention, Texas Department of State Health Services Austin, Texas, USA; [11]Arkansas Center for Birth Defects Research and Prevention, University of Arkansas for Medical Sciences, Little

Rock, Arkansas, USA; [12]Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

Address correspondence to Jeanette A. Stingone, Icahn School of Medicine at Mount Sinai, Department of Preventive Medicine, Box 1057, 17 East 102nd Street, 2nd Floor 2 West, New York, NY 10029 USA. Telephone: (212) 824-7368. E-mail:mailto:jeanette.stingone@mssm.edu

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Abstract

Background: Epidemiologic literature suggests exposure to air pollutants is associated with fetal development.

Objectives: To investigate maternal exposures to air pollutants during weeks two through eight of pregnancy and congenital heart defects.

Methods: Mothers from the National Birth Defects Prevention Study, a nine-state case-control study, were assigned one-week and seven-week averages of daily maximum concentrations of carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide and 24-hour measurements of fine and coarse particulate matter using the closest air monitor within 50 km to their residence during early pregnancy. Depending upon the pollutant, a maximum of 4632 live-birth controls and 3328 live-birth, fetal-death or electively terminated cases had exposure data. Hierarchical regression models, adjusted for maternal demographics, tobacco and alcohol use, were constructed. Principal component analysis was used to assess these relationships in a multipollutant context.

Results: Positive associations were observed between exposure to nitrogen dioxide and coarctation of the aorta and pulmonary valve stenosis. Exposure to fine particulate matter was positively associated with hypoplastic left heart syndrome but inversely associated with atrial septal defects. Examining individual exposure-weeks suggested associations between pollutants and defects that were not observed using the seven-week average. Associations between left ventricular outflow tract obstructions and nitrogen dioxide and hypoplastic left heart syndrome and particulate matter were supported by findings from the multipollutant analyses, although estimates were attenuated at the highest exposure levels.

Conclusions: Utilizing daily maximum pollutant levels and exploring individual exposure-weeks revealed some positive associations between certain pollutants and defects and suggested potential windows of susceptibility during pregnancy.

Introduction

Epidemiologic studies provide inconsistent evidence of an association between exposure to air pollutants and congenital heart defects (CHDs) (Agay-Shay et al. 2013; Dadvand et al. 2011a; Dadvand et al. 2011b; Dolk et al. 2010; Gilboa et al. 2005; Hansen et al. 2009; Padula et al. 2013; Rankin et al. 2009; Ritz et al. 2002; Strickland et al. 2009; Vrijheid et al. 2011). A recent meta-analysis identified two associations: nitrogen dioxide (NO_2) exposure and tetralogy of Fallot (TOF) and sulfur dioxide (SO_2) exposure and coarctation of the aorta (COA) (Vrijheid et al. 2011). However, only five defects/defect groupings were explored.

Most previous studies utilized monitoring data and assigned exposure by averaging daily pollutant averages over post-conception weeks three through eight. This method does not capture the temporal variability in exposure across windows with greater impact on cardiac development, which could mask or attenuate associations. Utilizing daily maximum concentrations, as opposed to averages, to calculate exposure would better capture daily exposure peaks and more closely parallel regulatory standards issued by the Environmental Protection Agency (EPA) (EPA 2012). Teratogenic models have suggested that environmental insults have a threshold below which there is no observed impact on the fetus (Dolk and Vrijheid 2003). Based on these past models of teratogenicity, the higher exposures represented by daily maxima could be more relevant to disruption of cardiac development. Separating a single overall average into weekly averages would also allow for the exploration of specific windows of susceptibility and reduce potential misclassification of exposure.

This study utilizes data from the National Birth Defects Prevention Study (NBDPS), a large population-based case-control study of birth defects, to investigate the association between CHDs in offspring and ambient concentrations of the following criteria air pollutants during

early pregnancy: carbon monoxide (CO), NO_2, ozone, particulate matter with aerodynamic diameter less than 10 micrometers (PM_{10}), particulate matter with aerodynamic diameter less than 2.5 micrometers ($PM_{2.5}$) and SO_2.

Methods

Study population

The NBDPS recruits cases from population-based, active surveillance congenital anomaly registries in nine US states and includes live births and stillbirths greater than 20 weeks gestation or at least 500 grams, as well as elective terminations of prenatally-diagnosed defects when available (Yoon et al. 2001). Arkansas, Iowa and Massachusetts ascertain cases statewide, while California, Georgia, New York, North Carolina, Texas and Utah ascertain cases in select counties. Cases are reviewed by clinical geneticists using standardized study-protocols to determine study eligibility and classification, and cases with chromosomal/microdeletion disorders and disorders of known single-gene deletion causation are excluded. Controls are unaffected livebirths who are randomly selected from vital records or hospital records, depending upon study center. The NBDPS has been approved by the institutional review boards (IRBs) of all participating centers, and all participants provided written or oral informed consent prior to participation. These analyses were reviewed and approved by the University of North Carolina IRB.

For this analysis, the study population consisted of all controls and eligible cases with a simple, isolated CHD (i.e. a single CHD with no extra-cardiac birth defects present) and an estimated date of delivery (i.e. due date) from 10/1/1997 through 12/31/2006. During this time period, the participation response was 69% among all cases and 65% for controls. Within the NBDPS, a team of clinicians with expertise in pediatric cardiology review information abstracted from the

medical record and centrally assign a single, detailed cardiac phenotype to each case whose diagnosis was confirmed by echocardiography, cardiac catheterization, surgery or autopsy and documented in the medical record. Phenotypes were then aggregated into individual CHDs and defect-groupings (Botto et al. 2007). The following additional groups were created due to limited sample size of individual defects: 1) other conotruncal defects, which included common truncus, interrupted aortic arch-type b, interrupted aortic arch-not otherwise specified (iaa-type b, iaa-nos), double outlet right ventricle associated with transposition of the great arteries (DORV-TGA) and not associated with TGA (DORV-other) and conoventricular septal defects (VSD-conoventricular); and 2) atresias that included both pulmonary and tricuspid atresia. Simple, isolated CHD cases represented 64% (N=12,383) of the total CHD cases. We restricted to offspring with a single CHD in order to create more etiologically homogeneous case groups, although this limits the generalizability of our findings. Women who reported having pregestational diabetes (Types I and II) during their pregnancy were excluded owing to the established association with CHD (Correa et al. 2008). Women living more than 50 km from a pollutant-specific air monitor were excluded from that analysis.

Exposure assignment

Each woman reported the due date that was provided by her clinician during pregnancy to obtain the gestational age of the infant at birth. Using the gestational age to estimate the date of conception, calendar dates were assigned to each week of pregnancy. Women's residential addresses during pregnancy were centrally geocoded to ensure consistency across study centers. Each geocoded address during weeks two through eight of pregnancy was matched to the closest air monitor for each pollutant with more than 50% of the data available using ArcGISv10 and

monitor locations obtained from EPA's Air Quality System. Participants from 1996-1998 were excluded from the analysis of $PM_{2.5}$ as monitoring began in 1999.

We used the daily maximum hourly measurement for CO, NO_2, and SO_2, the daily maximum 8-hour average for ozone, and 24-hour measurements of PM_{10} and $PM_{2.5}$ to assign exposure. We averaged over the daily maximum or 24-hour measurements for weeks two through eight of pregnancy to assign a seven-week and also one-week averages of the daily values. We included week two in addition to the standard window of cardiac development, due to the potential for lag effects of air pollution (van den Hooven et al. 2012). If only a single measurement was taken during a given week, it was assigned as the weekly exposure. Ambient levels of each pollutant except ozone were categorized into the following categories, using the distribution of pollutant concentration among controls: less than the 10^{th} centile (referent), 10^{th} centile to less than the median, the median to less than the 90^{th} centile and greater than or equal to the 90^{th} centile. These categories captured the departure from linearity observed in initial, exploratory analyses (data not shown). For similar reasons, ozone was categorized into quartiles. Centiles were calculated separately for the seven-week and one-week measures of exposure.

Statistical analysis

The following variables obtained from the maternal interview were identified as potential confounders through directed acyclic graph analysis (Greenland et al. 1999) and included in the final adjustment set: maternal age, race/ethnicity, educational attainment, household income, tobacco smoking in the first month of pregnancy, alcohol consumption during the first trimester, and maternal nativity. Maternal age was represented as a single, continuous term, measured at the time of conception. Race/ethnicity was self-reported and categorized into the following groups: White non-Latino, Black non-Latino, Latino, Asian or Pacific Islander and Other.

Educational attainment was collapsed into 6 categories: 0-6 years of education, 7-11 years, High School Graduate or Equivalency,1-3 years of college or trade school, 4 years of college or completion of a Bachelor's Degree and having an advanced degree. Household income was self-reported as less than $10,000 annually, more than $50,000 annually or in-between. We adjusted for any tobacco use in the first month of pregnancy and differentiated between some alcohol consumption (less than 4 drinks) and binge drinking (4 or more drinks) during the first trimester. Maternal nativity was defined as self-report of being born outside the United States.

To account for potential differences in case ascertainment by study center, models were also adjusted for the center-specific ratio of septal defects to total CHDs. Identifying septal defects is often dependent upon method of case ascertainment (Martin et al. 1989). All potential confounders, as well as distance to major roadway, pre-pregnancy body mass index, and maternal occupation status during pregnancy were assessed for effect measure modification by constructing logistic regression models with and without interaction terms and conducting likelihood ratio tests using an *a priori* alpha level of 0.1. Distance to the closest major road, defined as an interstate, US highway, state or larger county highway, was constructed using ArcGISv10 and then dichotomized at 50 meters. Pre-pregnancy body mass index was defined using self-reported maternal height and weight and categorized according to NIH guidelines into underweight ($BMI<18.5$), normal weight ($18.5\leq BMI<25$), overweight ($25\leq BMI<30$) and obese ($BMI\geq 30$). Maternal occupation status was defined as ever working outside the home during any time during pregnancy.

For each pollutant, models were constructed to explore individual defects and defect-groupings. If a woman did not have at least one monitoring value for each week of exposure, she was excluded from the weekly analysis. We explored the relationships between all weeks and all

defects, due to uncertainty in pregnancy dating when using an estimated date of conception and the lack of clearly elucidated mechanisms by which cardiac development could be disrupted by exposure to air pollution. Animal research suggests exposures outside the typical period of development for an individual heart structure could also be etiologically relevant (Morgan et al. 2008).

Because we simultaneously assessed multiple weeks of exposure and multiple defects/groupings, we constructed two-stage hierarchical regression models to account for the correlation between estimates and partially address multiple inference (Greenland 1992; Witte et al. 1998). The first-stage, represented in Equation 1, was an unconditional, polytomous logistic regression model of individual CHDs on exposure (*X)* defined as either all one-week averages of maximum or 24-hour pollutant values or the single 7-week average, and the full adjustment set (*w)* detailed above.

$$\Pr(Y = d|x, w) = \frac{\exp(\alpha_d + \boldsymbol{x\beta}_d + \boldsymbol{w\gamma}_d)}{1 + \sum_{k=1}^{m} \exp(\alpha_k + \boldsymbol{x\beta}_k + \boldsymbol{w\gamma}_k)} \quad [1]$$

β_d is the vector of regression coefficients corresponding to pollutant exposure for an individual CHD (*d*), while γ_d is the vector of regression coefficients corresponding to the covariates for a given defect, and *m* is the total number of individual types of CHDs. The second-stage model, which defines how the first-stage betas are associated, is given in Equation 2

$$\beta_i = Z_i\pi + \delta_i \quad [2]$$

where Z_i is a row in the design matrix that includes an intercept term and then indicator variables for type of defect, broader defect grouping, and exposure week/level for the i-th β, π is the vector of coefficients corresponding to the variables included in the design matrix and δ_i are independent normal random variables with a mean of zero and a variance of τ^2 that describe the

residual variation in β_i. The obtained second-stage coefficients,π, are used to estimate values toward which the first-stage coefficients will be shrunk, with the magnitude of the shrinkage depending upon the precision of the maximum likelihood estimate obtained in stage 1 and the value of the second stage variance, τ^2 (Greenland 1992; Witte et al. 1994). We fixed τ^2 at 0.5, corresponding to a prior belief with 95% certainty that the residual odds ratio will fall within a 16-fold span.

To assess whether our results were robust to changes in model specification we conducted sensitivity analyses by setting the value of τ^2 to 0.25, corresponding to a 7-fold odds ratio span, as well as to a value of 1, corresponding to a 50-fold span. We also explored different specifications for the design matrix, in turn defining the prior value as a common mean for all defects, a common mean for each defect, or a common mean for each exposure week/level, across defects. Individual defects with more than 10 but fewer than 100 cases were excluded from hierarchical models and explored using Firth's penalized maximum likelihood method to address the quasi-complete separation that occurred due to small sample size (Heinze and Schemper 2002). These defects included the individual defects collapsed into the other conotruncals and atresia categories described above, Ebstein's Anomaly which was part of the right ventricular outflow tract obstruction (RVOTO) defect-grouping, and muscular ventricular septal defects ($VSD_{muscular}$) which was part of the septal defect-grouping. Interrupted aortic arch-type A and partial anomalous pulmonary venous return had fewer than 10 cases each and were excluded from all individual analyses but were included in the left ventricular outflow tract obstruction (LVOTO) and anomalous pulmonary venous return (APVR) defect-groupings respectively. To assess whether pollutant-defect relationships conformed to a monotonic dose-response, we reanalyzed the data using incremental coding which compares each category of exposure to its immediate

predecessor. If the incremental ORs are all above (or below) 1, the relationship conforms to a monotonic dose-response (Maclure and Greenland 1992).

To explore associations with CHDs within a multipollutant context, a principal component analysis (PCA) was conducted among participants who lived within 50 km of each type of monitor. PCA is used to reduce the number of correlated variables into a smaller number of artificial variables that capture most of the variance of the original variables while being uncorrelated with each other (Hatcher 1994). This allows the resulting factors to be included within the same model, reducing issues of multicollinearity. Applying PCA, we retained components that accounted for at least the same or more variance than one of the original pollutant variables. We then applied a varimax rotation and calculated factor scores for each participant. These factor scores were categorized using the 10^{th}, 50^{th} and 90^{th} centiles and used to assign exposure in hierarchical models.

Results

Demographics of the NBDPS controls and CHD defect-groupings providing residential address information and eligible to be matched to the closest air monitor for each pollutant are presented in Table 1. Case distribution varied by study-site, particularly for the septal defect grouping. The ratios used to adjust for case-ascertainment differences by site are located in the Supplemental Material, Table S1. The percentage of women who lived 50 km from an air pollution monitor varied from 56% for SO_2 to 73% for PM_{10}. Demographics were similar across the pollutant-specific populations, although women who lived within 50 km of a SO_2 monitor were slightly older and were more likely to be White or African-American, work outside the home, have higher household income and report alcohol consumption during pregnancy. (data not shown). The number of cases/controls by exposure distribution for each pollutant are represented in Table

2, along with the pollutant levels that were used to define exposure categories. Median distance to the monitor was similar across pollutants, although women tended to live further from SO_2 monitors and closer to $PM_{2.5}$ monitors.

Exposure assigned as a single 7-week average of daily maxima or 24-hour measurements

Figure 1 shows the estimated adjusted odds ratios (OR) and 95% confidence intervals (CI) resulting from the hierarchical regression models of the 7-week average exposure to individual pollutants and CHDs (see Supplemental Material, Table S2 for corresponding numerical data). Crude estimates were similar to estimates adjusted for confounders (data not shown). Larger ORs were observed with greater NO_2 exposure for individual defects within the LVOTO and RVOTO groupings. Women with the highest average daily maximum exposure to NO_2 (greater than 45.5 ppb) had more than two times the odds of both COA (OR 2.5; 95% CI: 1.21, 5.18) and PVS (OR 2.03; 95%CI: 1.23, 3.33) as women with the lowest exposure (less than 18.9 ppb). We observed a positive association between SO_2 exposure and PVS, although it was attenuated at the highest exposure level (OR 10-50/10 centile contrast 2.34; 95% CI: 1.33, 4.14; OR 50-90/10 centile contrast 2.06; 95% CI: 1.16, 3.67; OR 90/10 centile contrast 1.48; 95% CI: 0.74, 2.97). Hypoplastic left heart syndrome (HLHS) was associated with exposure to $PM_{2.5}$ (90/10 centile contrast: OR 2.04; 95% CI: 1.07, 3.89) but not NO_2. We observed increased odds of perimembranous ventricular septal defects (VSD_{pm}) (OR 90/10 centile contrast 1.48; 95% CI: 0.91 2.42) and reduced odds of atrial septal defects (ASD) (OR 90/10 centile contrast 0.67; 95% CI: 0.41, 1.09) with SO_2 exposure. We also observed reduced odds of ASDs with exposure to $PM_{2.5}$ (OR 50-90/10 contrast 0.50; 95% CI: 0.38, 0.65; OR 90/10 contrast 0.54; 95% CI: 0.35, 0.81). Although imprecise, the effect estimates for APVR and CO and NO_2 exposures indicated lower odds with greater exposure, although the negative association was attenuated at the highest

exposure level. The associations between NO_2 and PVS, NO_2 and COA, SO_2 and VSD_{pm} and SO_2 and ASDs increased monotonically with increasing exposure (data not shown). For both PM_{10} and NO_2, we found evidence of effect measure modification by distance to a major road in first-stage maximum likelihood models, using our *a priori* criterion of a likelihood ratio test p-value less than 0.1 (PM_{10} likelihood ratio test: χ^2 =30.5, p=0.03; NO_2 likelihood ratio test: χ^2=34.5, p=0.01). In both cases, odds ratios were generally greater for women who lived within 50 meters of a roadway (Supplemental Material, Table S3).

Exposure assigned as one-week average of daily maxima or 24-hour measurements

Full results for the weekly exposure analyses are provided in Supplemental Material, Table S4. PVS showed variability within the window of cardiac development for multiple pollutants (Figure 2). Both CO and ozone had individual weeks where the estimates were larger in magnitude than estimates obtained using the summary exposure and where the other weeks were closer to null, suggesting a period of greater susceptibility (CO-week 2: 90/10 centile comparison: OR 0.37; 95% CI: 0.19,0.7; ozone-week 3 75/25 centile comparison: OR 2.15; 95% CI: 1.22, 3.78). $PM_{2.5}$ had no association with PVS when using a summary measure of exposure, but there was an almost doubling of odds in week 5 when comparing women with exposure greater than the 90th centile to women with exposure less than the 10th centile (OR 1.83; 95% CI: 1.08, 3.12) that was similarly observed in week 8.

Week 2 of pregnancy was another potential window of susceptibility to $PM_{2.5}$. Women having a child with TOF had almost twice the odds of being above the 90th centile versus below the 10th centile for $PM_{2.5}$ exposure in week 2 of pregnancy as controls (OR 1.96; 95% CI: 1.11, 3.46) while women with a baby with atrioventricular septal defect (AVSD) had more than three times the odds (OR 3.43; 95% CI: 1.36, 8.66). Women with offspring with defects within the septal

grouping were less likely to have higher $PM_{2.5}$ exposure during this time (90/10 centile comparison OR 0.6; 95% CI: 0.4, 0.9). Using the summary exposure revealed a slightly elevated odds ratio for VSD_{pm} among women with SO_2 exposure greater than the 90^{th} centile (OR 1.48; 95%CI 0.91, 2.42), but weekly analysis revealed this association was limited to week 3 and the magnitude increased (VSD_{pm} OR 1.98; 95% CI: 1.1, 3.56). During other weeks, the ORs for VSD_{pm} comparing the 90^{th} centile to the 10^{th} centile ranged from 0.77-1.13.

Principal component analysis

Only 26% of the geocoded population (N=2914) had exposure data for all pollutants. These women were primarily from the Massachusetts and Atlanta sites, non-smokers, and living in a higher income household. African-American women made up a slightly larger percentage of these women when compared to the individual pollutant populations (data not shown). Using this subsample, three factors emerged from the principal component analysis. The factor that explained the largest amount of variance was loaded primarily by CO and NO_2, gaseous pollutants likely related to direct emissions from local sources such as motor vehicle traffic. The second factor, driven by PM_{10}, $PM_{2.5}$ and ozone represents local particulates and secondary pollutant generation. The third factor was loaded by SO_2 and most likely represents emissions from regional sources, potentially from coal combustion.

Findings were less precise than single-pollutant models due to the reduced sample size (Figure 3; Supplemental Material, Table S5, for corresponding numeric data). We observed odds ratios greater than 1 for the NO_2 loaded factor (factor 1) and LVOTO defects, particularly aortic stenosis and HLHS and the PM_{10}/$PM_{2.5}$/ozone factor (factor 2) and HLHS, although these associations were diminished or absent at the highest exposure level. The odds ratios for the NO_2 loaded factor (factor 1) and PVS were attenuated when compared to results from the NO_2 single-

pollutant model. We also observed monotonically, increasing odds ratios between PVS and exposure to the PM_{10}/$PM_{2.5}$/ozone factor (factor 2), which was not observed in any of the single-pollutant models for those individual pollutants. Within the multipollutant context, the SO_2 loaded factor (factor 3) was inversely associated with the septal defect grouping, as well as both ASD and VSD_{pm} . In the single-pollutant models, we had observed a slight inverse association with ASD, but a slightly positive association with VSD_{pm}. The slightly increased odds ratios for SO_2 exposure and PVS and HLHS observed in the single-pollutant model were not observed in the results from the principal component analysis.

The sensitivity analysis to explore the effects of model specification did not show a material difference in results obtained when using different values of second-stage variance or varying factors defining the predicted values (data not shown). To explore our choice of a 50 km buffer size, we restricted our analyses to women who lived within 10 km of a monitor and used the same exposure categories and model construction described previously (Supplemental Material, Table S6). Sample size was reduced to 27.5-48.1% (N=1683-3709) of the original study population depending upon pollutant. Despite the greater imprecision, many estimates remained similar, for example the observed positive associations in the full population between higher exposure to NO_2 and LVOTO (OR 1.53; 95%CI 0.98,2.39) and RVOTO defects (OR 2.22; 95% CI 1.40, 3.52) were only slightly changed when restricting to the population within 10 km of an air monitor (LVOTO OR 1.44; 95% CI 0.58, 3.61; RVOTO OR 2.33; 95% CI 0.75, 7.22). The inverse association between $PM_{2.5}$ exposure and the septal defect grouping also remained consistent after limiting the population. Although most null estimates remained so, some null estimates increased in magnitude, suggesting a potential for an association in the restricted population. For example, the OR for LVOTO defects comparing the highest and lowest quartiles

of ozone exposure was 0.94 in the population within 50 km of a monitor (95% CI: 0.73, 1.22) but was 1.62 (95% CI: 0.84, 3.13) in the population within 10 km of a monitor. A similar increase in magnitude was observed for $PM_{2.5}$ and LVOTO defects. The estimates related to SO_2 exposure changed the most, with multiple ORs greater than 1 in the population of women living within 50 km of a monitor crossing over the null when the population was restricted to those within 10 km.

Discussion

We found the odds of several CHDs were higher among women with greater exposures to criteria air pollutants. We observed monotonically increasing associations between nitrogen dioxide exposure and both COA and PVS. We also observed that women with a child with HLHS were two times as likely to live in an area with the highest level of $PM_{2.5}$ exposure as women whose child did not have a CHD, although a similar association was not seen for women in the middle-high exposure level. Utilizing one-week averages, we observed temporal variability in odds of certain CHDs within the window of cardiac development. Marked by positive or negative associations in individual weeks with near null relationships in the other weeks, this pattern was observed for AVSD, PVS, TOF and the septal defect-grouping when looking across weeks of $PM_{2.5}$ exposure, PVS when examining weeks of ozone exposure, and VSD_{pm} across weeks of SO_2 exposure, although we did not observe a consistent week of greater susceptibility across different defects and pollutants.

Our findings suggest preliminary evidence that there may be periods of higher or lower susceptibility within the window of cardiac development. Embryological evidence indicates the timing of specific stages of cardiac development, beginning with the migration of cells to form the endocardial tubes and culminating with the septation of the ventricles and outflow tracts in weeks 7 and 8 of development (Gittenberger-de Groot et al. 2005). However, there is

experimental research showing that triggering oxidative stress in diabetic-mice can result in apoptosis among migrating neural crest cells which later results in outflow tract defects (Morgan et al. 2008) and that neural crest cells enable the endocardial cushions to form the cardiac valves (Jain et al. 2011). This suggests it is possible that pollutant-induced oxidative stress in earlier weeks of development can trigger similar disruptions in neural crest cells which later impact development of cardiac structures and that windows of susceptibility to environmental insults may not always directly coincide with the established stages of fetal heart development. Further research is needed to explore how timing of exposure within this narrow window may impact the risk of CHDs or whether the fluctuations in results we observed when examining weekly exposure are due to random noise.

Findings from the PCA-based analysis continued to show greater odds of certain CHDs with increasing pollutant exposure. The inverse association between SO_2 and ASDs observed in the single-pollutant analysis was also observed in the PCA-based analysis. However, the positive associations between exposure to SO_2 and PVS and VSD_{pm} found in the single-pollutant analysis were not observed when the SO_2 loaded component was examined simultaneously with other pollutant components. These differences could be due to co-pollutants not accounted for in the single-pollutant models or to different demographics of the subsample of women with data on all pollutants. We often observed a decrease in odds at the highest ambient level, compared to the median-high group, in both the PCA-based analyses and single-pollutant models. Ritz has previously suggested this non-linearity could be due to differential pregnancy loss at very high exposures (Ritz 2010). It is also possible that women who live in highly polluted areas spend less time outdoors, causing exposure to be lower than what the ambient level suggests.

Our findings were consistent with the primary associations reported in the previous meta-analysis, NO_2 and TOF, and SO_2 and COA, as well as an association between greater NO_2 exposure and COA which was suggested in the meta-analysis, although not robust to the exclusion of the largest study (Vrijheid et al. 2011). We observed some of the findings from individual studies that were not identified in the meta-analysis; for example, we observed the association between SO_2 and VSDs reported by Gilboa et al. (2005) and the inverse association between $PM_{2.5}$ and ASDs reported by Padula et al. (2013) but not other findings such as the inverse associations between SO_2 and conotruncal defects reported by both Gilboa et al. (2005) and Hansen et al. (2009). Differences in findings between studies could be due to spatial variation in source of pollutants and composition of particulates, as well as differences in case ascertainment and exposure assignment (Vrijheid et al. 2011).

This study has a number of strengths, including the large geographic scope and sample size of the NBDPS that allows analysis of systematically classified individual CHDs, while limiting analyses to simple, isolated defects to avoid heterogeneity from etiologies of multiple defects. Including live-births, fetal deaths, and elective terminations prevents incomplete case ascertainment, and collecting complete residential history, avoids misclassification of exposure due to using residence at delivery (Miller et al. 2010). We explored timing of exposure within the critical window of heart development and utilized daily maxima so as not to smooth over potentially relevant variability in exposure. Utilizing hierarchical regression allowed us to improve estimation and partially address the issue of multiple testing, while utilizing principal component analysis allowed us to assess the relationship between air pollutants and CHDs in a multipollutant context.

Assigning exposure using ambient concentrations of pollutants at their residential location does not account for time spent indoors and pollutant concentrations at other relevant locations. This exposure misclassification could impact our effect estimates if there are differences in these factors between cases and controls, for example if women of case offspring had more difficult pregnancies, limiting their outdoor movement. There is also the potential for exposure misclassification by assigning exposure using the nearest monitor. Previous research suggests that even when limiting to the closest monitor within 10 km, the 10^{th}–90^{th} percentile exposure contrast is larger for nearest monitor analyses than other forms of exposure assessment (Marshall et al. 2008). This would have less of an impact on our study where we categorized exposure based on the distribution, rather than performing contrasts on a fixed-unit change in exposure. In simulation analyses of air pollution and incidence of cardiovascular events, Kim et al found that hazard ratios obtained using nearest-monitor exposures were more biased than those obtained using exposures obtained from kriging particularly as the monitoring network became sparse (Kim et al. 2009). These biases tended to be toward the null, suggesting our estimates may underestimate the true relationship between air pollutants and CHDs.

The NBDPS had a response slightly lower than 70% and is subject to potential selection bias based on who agrees to participate. Additionally, there is the potential for selection bias if the factors that contribute to women living near a pollutant monitor are also associated with pollutant exposure and CHDs. We did not observe strong associations between maternal demographic factors that could influence residential location and the presence of CHDs within our full population. However, our results may not be generalizable to populations that live more than 50 km from an air monitor. Because air pollutants vary spatially, study center may confound the relationship between air pollutants and CHDs through pathways such as differences in case

ascertainment and resident sociodemographics. We controlled for a marker of case ascertainment in our model, but we may not have completely accounted for differences in case ascertainment across sites, and residual confounding due to unmeasured, spatially varying factors including other environmental exposures, could impact our results. Our PCA analysis was based on a highly select population who lives near multiple pollutant monitors and may not be generalizable to the larger population.

We conducted many analytic contrasts, and although hierarchical regression partially addresses multiple comparisons, it is possible that some of our findings are due to chance. We utilized hierarchical regression because other methods which deal with multiple comparisons do not account for the association between estimates that occurs when assessing weekly exposures simultaneously. It is possible that certain subgroups in the population may be more vulnerable to the impacts of air pollution due to their diet, genetics, co-exposures or other factors which we did not address in this study. If this is the case, we may have underestimated or missed an association between air pollutants and CHDs that would only be seen in that select population.

In this study, we observed increased odds of several CHDs with greater pollutant exposure. Some of these positive associations were observed only during specific weeks within the window of cardiac development, suggesting that accounting for temporal variability in pollutant concentrations and developmental susceptibility can improve effect estimation. Future research should focus on further exploration of temporal windows of susceptibility and examining the risk of CHDs within a multipollutant context, in order to gain understanding of the contribution of the different air pollutants.

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Table 1: Demographic characteristics of geocoded, non-pregestational diabetic population of congenital heart defect-groupings and controls, National Birth Defects Prevention Study (1997-2006). Values are n (%) unless otherwise noted.

Demographics	Controls	APVR	AVSD	Conotruncal	LVOTO	RVOTO	Septal
Site							
Arkansas	611 (9.7)	18 (11.6)	10 (12.2)	89 (8.9)	66 (8.0)	110 (15.1)	321 (17.4)
California	871 (13.8)	27 (17.4)	5 (6.1)	159 (15.8)	111 (13.4)	60 (8.3)	110 (6.0)
Iowa	806 (12.7)	10 (6.5)	15 (18.3)	96 (9.6)	122 (14.7)	95 (13.1)	189 (10.2)
Massachusetts	916 (14.5)	28 (18.1)	15 (18.3)	187 (18.7)	117 (14.1)	121 (16.6)	240 (13.0)
Metro Atlanta	750 (11.9)	19 (12.3)	11 (13.4)	140 (13.9)	99 (11.9)	92 (12.6)	231 (12.5)
New York	637 (10.1)	13 (8.4)	7 (8.5)	110 (11.0)	86 (10.4)	68 (9.3)	125 (6.8)
North Carolina	452 (7.1)	8 (5.2)	4 (4.9)	56 (5.6)	27 (3.3)	33 (4.5)	74 (4.0)
Texas	815 (12.9)	20 (12.9)	7 (8.5)	115 (11.5)	88 (10.6)	66 (9.1)	439 (23.8)
Utah	470 (7.4)	12 (7.7)	8 (9.8)	52 (5.2)	113 (13.6)	83 (11.4)	119 (6.5)
Race/ethnicity							
White, Non-Latino	3797 (60.0)	89 (57.4)	62 (75.6)	612 (61.0)	592 (71.4)	474 (65.1)	1032 (55.8)
Black, Non-Latino	682 (10.8)	9 (5.8)	10 (12.2)	102 (10.2)	50 (6.0)	98 (13.5)	238 (12.9)
Latino	1460 (23.1)	44 (28.4)	4 (4.9)	221 (22.0)	159 (19.2)	116 (15.9)	467 (25.3)
Asian/Pac Islander	168 (2.7)	7 (4.5)	3 (3.7)	35 (3.5)	13 (1.6)	13 (1.8)	53 (2.9)
Other	219 (3.5)	6 (3.9)	3 (3.7)	34 (3.4)	15 (1.8)	27 (3.7)	58 (3.1)
Education							
0-6 years	210 (3.3)	7 (4.6)	1 (1.2)	40 (4.0)	27 (3.3)	19 (2.6)	58 (3.1)
7-11 years	844 (13.4)	25 (16.3)	6 (7.3)	121 (12.1)	99 (12.0)	81 (11.1)	293 (15.9)
High school diploma or equivalent	1516 (24.1)	37 (24.2)	20 (24.4)	239 (23.9)	186 (22.5)	196 (26.9)	452 (24.5)
1-3 years college or trade school	1726 (27.4)	42 (27.5)	29 (35.4)	276 (27.6)	227 (27.4)	196 (26.9)	551 (29.8)
4 years college or Bachelors degree	1414 (22.5)	30 (19.6)	20 (24.4)	229 (22.9)	216 (26.1)	181 (24.9)	367 (19.9)
Advanced degree	581 (9.2)	12 (7.8)	6 (7.3)	95 (9.5)	73 (8.8)	55 (7.6)	126 (6.8)
Maternal age, mean (sd)	27.0 (6.1)	26.7 (6.7)	26.9 (5.3)	27.8 (6.2)	27.8 (5.8)	27.7 (6.1)	27.0 (6.5)
Nativity							
Born in US	5110 (81.2)	118 (77.1)	70 (85.4)	804 (80.4)	697 (84.2)	633 (87.0)	1527 (82.7)

Demographics	Controls	APVR	AVSD	Conotruncal	LVOTO	RVOTO	Septal
Household income							
<$10,000	1066 (18.5)	26 (19.1)	13 (16.5)	167 (17.7)	105 (13.5)	109 (16.1)	351 (20.4)
$10,000-$50,000	2695 (46.7)	69 (50.7)	41 (51.9)	410 (43.4)	368 (47.2)	321 (47.4)	853 (49.7)
>$50,000	2012 (34.9)	41 (30.2)	25 (31.7)	367 (38.9)	306 (39.3)	248 (36.6)	514 (29.9)
Occupational status							
Worked outside home	4545 (72.1)	97 (63.4)	70 (85.4)	742 (74.2)	604 (72.9)	544 (74.7)	1279 (69.3)
Smoking							
First month	967 (15.3)	26 (17.0)	26 (31.7)	140 (14.0)	114 (13.8)	122 (16.8)	373 (20.2)
Alcohol consumption							
No drinking	3981 (63.6)	101 (67.3)	50 (61.0)	603 (60.9)	550 (66.9)	473 (66.2)	1210 (65.9)
<4 drinks	1509 (24.1)	31 (20.7)	19 (23.2)	251 (25.3)	165 (20.1)	164 (22.9)	405 (22.1)
≥4 drinks	770 (12.3)	18 (12.0)	13 (15.9)	137 (13.8)	107 (13.0)	78 (10.9)	222 (12.1)
Body mass index							
BMI<18.5 underweight	316 (5.2)	8 (5.4)	4 (5.0)	50 (5.2)	34 (4.3)	25 (3.6)	96 (5.4)
18.5≤BMI<25 normal	3373 (55.4)	79 (53.7)	46 (57.5)	519 (53.5)	426 (53.8)	330 (46.9)	910 (51.0)
25≤BMI<30 overweight	1404 (23.1)	31 (21.1)	18 (22.5)	221 (22.8)	182 (23.0)	190 (27.0)	425 (23.8)
BMI≥30 obese	993 (16.3)	29 (19.7)	12 (15.0)	180 (18.6)	150 (18.9)	159 (22.6)	354 (19.8)
Proximity to roadway							
<50 meters	1168 (18.5)	37 (23.9)	14 (17.1)	192 (19.1)	156 (18.8)	112 (15.4)	331 (17.9)

Table 2: Congenital heart cases and controls by exposure level of criteria air pollutants, National Birth Defects Prevention Study (1997-2006, except for $PM_{2.5}$ 1999-2006).

Pollutant and Outcome	<10th centile	10th-<50th centile	50th-<90th centile	≥90th centile	Distance to Monitor 25th,50th,75th centile (km)
CO (ppm)	<0.58	0.58-<1.16	1.16-<2.13	≥2.13	7.0, 14.8, 26.5
Controls (n)	434	1740	1739	436	
All cases (n)	271	1202	1235	308	
LVOTO (n)[a]	53	249	229	49	
Aortic stenosis (n)	12	50	45	10	
COA (n)	22	106	80	21	
HLHS (n)	18	91	102	17	
Conotruncal	66	305	312	70	
d-TGA	22	102	102	21	
TOF	33	162	167	37	
Other conotruncals	11	41	43	12	
APVR[b]	17	42	36	10	
TAPVR	15	42	29	10	
AVSD	5	20	25	3	
RVOTO[c]	46	202	207	47	
Pulmonary/tricuspid atresia	12	41	39	9	
PVS	33	142	154	36	
Septal[d]	84	382	424	128	
VSD_{pm}	47	185	215	54	
ASD	36	172	159	49	
NO_2 (ppb)	<18.9	18.9-<33.3	33.3-<45.5	≥45.5	6.8, 13.7, 25.1
Controls (n)	396	1584	1591	397	
All cases (n)	248	1088	1152	309	
LVOTO[a] (n)	43	211	235	56	
Aortic stenosis (n)	7	47	42	14	
COA (n)	12	74	103	26	
HLHS (n)	23	86	89	16	
Conotruncal	58	277	285	71	
d-TGA	23	92	99	24	
TOF	27	150	140	38	
Other conotruncals	8	35	46	9	
APVR[b]	16	36	35	13	
TAPVR	15	33	32	13	
AVSD	9	18	22	4	
RVOTO[c]	38	164	194	63	
Pulmonary/tricuspid atresia	6	41	34	9	
PVS	32	109	143	50	
Septal[d]	84	380	379	101	
VSD_{pm}	43	178	189	51	
ASD	36	163	161	35	

Pollutant and Outcome	<10th centile	10th-<50th centile	50th-<90th centile	≥90th centile	Distance to Monitor 25th,50th,75th centile (km)
O_3 (ppb)[e]	<32.2	32.2-<42.9	42.9-<51.8	≥51.8	6.8, 12.8, 21.9
Controls (n)	442	1769	1768	443	
All cases (n)	308	1311	1204	269	
LVOTO[a] (n)	60	228	223	55	
Aortic stenosis (n)	9	47	48	8	
COA (n)	23	86	87	27	
HLHS (n)	27	92	85	20	
Conotruncal	85	300	283	68	
d-TGA	31	92	112	19	
TOF	42	169	135	40	
Other conotruncals	12	39	36	9	
APVR[b]	8	45	47	12	
TAPVR	7	41	45	11	
AVSD	6	17	22	4	
RVOTO[c]	38	196	202	51	
Pulmonary/tricuspid atresia	7	41	40	10	
PVS	25	142	147	36	
Septal[d]	109	523	427	79	
VSD_{pm}	47	203	200	45	
ASD	44	279	196	31	
PM_{10} (μg/m^3)	<14.9	14.9-<24.2	24.2-<40.6	≥40.6	6.0, 13.5, 25.2
Controls (n)	462	1853	1853	464	
All cases (n)	298	1377	1387	271	
LVOTO[a] (n)	54	229	276	52	
Aortic stenosis (n)	12	54	63	8	
COA (n)	15	97	97	22	
HLHS (n)	24	76	115	21	
Conotruncal	64	295	311	87	
d-TGA	25	97	98	32	
TOF	33	150	175	43	
Other conotruncals	6	48	38	12	
APVR[b]	8	52	45	13	
TAPVR	8	45	39	13	
AVSD	2	25	24	4	
RVOTO[c]	55	202	225	40	
Pulmonary/tricuspid atresia	16	40	46	6	
PVS	33	151	164	29	
Septal[d]	115	572	503	75	
VSD_{pm}	44	227	214	37	
ASD	56	292	233	36	
$PM_{2.5}$ (μg/m^3)	<7.77	7.77-<12.1	12.1-<19.7	≥19.7	5.3, 10.4, 20.7
Controls (n)	440	1763	1763	441	
All cases (n)	378	1420	1212	301	

Pollutant and Outcome	<10th centile	10th-<50th centile	50th-<90th centile	≥90th centile	Distance to Monitor 25th,50th,75th centile (km)
LVOTO[a] (n)	66	250	207	73	
Aortic stenosis (n)	21	61	39	14	
COA (n)	28	92	88	25	
HLHS (n)	15	95	77	33	
Conotruncal	71	287	291	87	
d-TGA	25	90	95	25	
TOF	35	150	161	50	
Other conotruncals	11	47	35	12	
APVR[b]	14	51	36	13	
TAPVR	12	46	32	11	
AVSD	3	26	27	6	
RVOTO[c]	58	206	229	47	
Pulmonary/tricuspid atresia	14	46	34	11	
PVS	39	143	178	35	
Septal[d]	166	600	418	75	
VSD_{pm}	49	229	222	38	
ASD	115	369	189	36	
SO_2 (ppb)	<3.45	3.45-<9.7	9.7-<19.9	≥19.9	8.9, 18.8, 30.2
Controls (n)	350	1403	1404	351	
All cases (n)	231	1048	1098	240	
LVOTO[a] (n)	33	190	200	39	
Aortic stenosis (n)	9	39	32	7	
COA (n)	13	69	92	21	
HLHS (n)	10	81	72	11	
Conotruncal	48	221	258	60	
d-TGA	16	76	87	21	
TOF	24	117	133	33	
Other conotruncals	8	28	38	6	
APVR[b]	9	33	35	7	
TAPVR	9	27	32	6	
AVSD	3	14	21	8	
RVOTO[c]	26	203	183	31	
Pulmonary/tricuspid atresia	8	37	35	5	
PVS	15	155	135	22	
Septal[d]	112	387	398	93	
VSD_{pm}	33	164	192	49	
ASD	76	196	151	29	

Abbreviations: APVR-anomalous pulmonary venous return; ASD-atrial septal defect; AVSD-atrioventricular septal defect; CO-carbon monoxide; COA-coarctation of the aorta; d-TGA-d-transposition of the great arteries; HLHS-hypoplastic left heart syndrome; LVOTO-left ventricular outflow tract obstructions; NO_2-nitrogen dioxide; O_3-ozone; PM_{10}-particulate matter less than 10 microns in diameter;

$PM_{2.5}$-particulate matter less than 2.5 microns in diameter; PVS-pulmonary valve stenosis; RVOTO-right ventricular outflow tract obstructions; SO_2-sulfur dioxide; TAPVR-total anomalous pulmonary venous return; TOF-tetralogy of Fallot; VSD_{pm}-perimembranous ventricular septal defects.

[a]LVOTO grouping also includes cases of interrupted aortic arch, type A which was not analyzed individually due to limited sample size. [b]APVR grouping also includes cases of partial anomalous pulmonary venous return, which was not analyzed individually due to limited sample size. [c]RVOTO grouping also includes cases of Ebstein's Anomaly which was not analyzed individually in the hierarchical analysis due to limited sample size. [d]Septal grouping also includes cases of muscular ventricular septal defects ($VSD_{muscular}$) which was not analyzed individually in the hierarchical analysis due to limited sample size. The exception is $PM_{2.5}$ as $VSD_{muscular}$ were only collected in the first year of the study when $PM_{2.5}$ measurements were not available. [e]Ozone (O_3) exposure was categorized into quartiles using the distribution among the controls. The referent was $<25^{th}$ percentile, and the other 3 categories were 25-<50, 50-<75, and 75+.

Figure legends

Figure 1: Estimated adjusted odds ratios and 95% confidence intervals between congenital heart defects and 7-week average of daily maxima/24 hour measures of criteria air pollutants, National Birth Defects Prevention Study 1997-2006 (for fine particulate matter ($PM_{2.5}$) 1999-2006); Abbreviations: APVR-anomalous pulmonary venous return; ASD-atrial septal defect; AVSD- atrioventricular septal defect; CO-carbon monoxide; COA-coarctation of the aorta; d-TGA-d-transposition of the great arteries; HLHS-hypoplastic left heart syndrome; LVOTO-left ventricular outflow tract obstructions; NO_2-nitrogen dioxide; O_3-ozone; PM_{10}-particulate matter less than 10 microns in diameter; $PM_{2.5}$-particulate matter less than 2.5 microns in diameter; PVS-pulmonary valve stenosis; RVOTO-right ventricular outflow tract obstructions; SO_2-sulfur dioxide; TAPVR-total anomalous pulmonary venous return; TOF-tetralogy of Fallot; VSD_{pm}-perimembranous ventricular septal defects. Other conotruncal category includes common truncus, interrupted aortic-arch, type B and type not specified, double outlet right ventricle defects, and conoventricular septal defects. A double slash, '//' indicates truncation of the results. Squares indicate defect-groupings; circles indicate individual defects. Defect-groupings include all individual defects listed underneath with the following additions: LVOTO interrupted aortic arch-type A; APVR-partial APVR; RVOTO-Ebstein's Anomaly; Septal-muscular venricular septal defects ($VSD_{muscular}$), except for $PM_{2.5}$. $VSD_{muscular}$ were only collected in the first year of study when there was no available $PM_{2.5}$ data. Those defects could not be analyzed within the hierarchical regression due to limited sample size. Odds ratios estimated from hierarchical regression models. First stage was a polytomous logistic model, adjusted for maternal race/ethnicity, age educational attainment, household income, maternal smoking status and alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio. Second stage was a linear model with indicator variables for defect, defect grouping and level of exposure. For all pollutants except ozone, the three categories of exposure are: 10^{th} centile to less than the 50^{th} centile (10-<50), 50^{th} centile to less than the 90^{th} centile (50-<90), at or

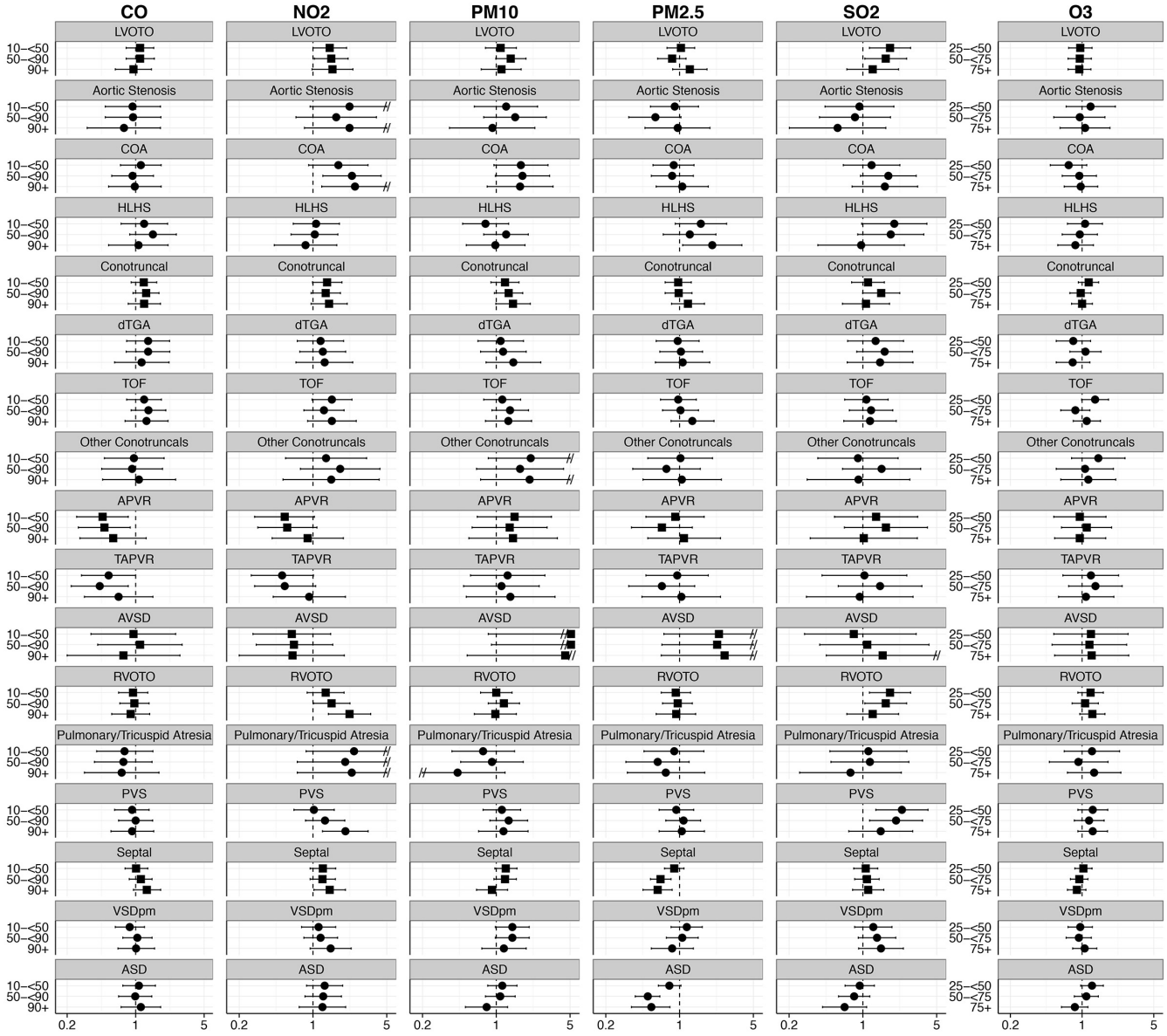
greater than the 90th centile (90+), with the referent level being less than the 10th centile among controls. For ozone, the three categories of exposure were 25th to less than the 50th centile, 50th centile to less than the 75th centile, at or greater than the 75th centile, with the referent grouping being below the 25th centile. Pollutant levels which define the category cutpoints are provided in Table 2. See Supplemental Material, Table S2, for corresponding numeric data.

Figure 2: Estimated adjusted odds ratios and 95% confidence intervals of pulmonary valve stenosis for categorical measures of one-week averages of daily maxima/24 hour measures of criteria air pollutants, plotted for weeks 2 through 8 of pregnancy National Birth Defects Prevention Study 1997-2006 (for fine particulate matter ($PM_{2.5}$) 1999-2006).Abbreviations: CO-carbon monoxide; NO_2-nitrogen dioxide; O_3-ozone; PM_{10}-particulate matter less than 10 microns in diameter; $PM_{2.5}$-particulate matter less than 2.5 microns in diameter; SO_2-sulfur dioxide; Odds ratios estimated from hierarchical regression models. First stage was a polytomous logistic model, adjusted for maternal race/ethnicity, age educational attainment, household income, maternal smoking status and alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio. Second stage was a linear model with indicator variables for defect, defect grouping and level of exposure. For all pollutants except ozone, the three categories of exposure are: 10th centile to less than the 50th centile (10-<50), 50th centile to less than the 90th centile (50-<90), at or greater than the 90th centile (90+), with the referent level being less than the 10th centile among controls. For ozone, the three categories of exposure were 25th to less than the 50th centile, 50th centile to less than the 75th centile, at or greater than the 75th centile, with the referent grouping being below the 25th centile. Pollutant levels which define the category cutpoints are provided in Table 2. See Supplemental Material, Table S4, for corresponding numeric data.

Figure 3: Estimated adjusted odds ratios and 95% confidence intervals between congenital heart defects and pollutant factors identified through principal components analysis within the National Birth Defects Prevention Study, 1999-2006. Abbreviations: APVR-anomalous pulmonary venous return; ASD-atrial

septal defect; AVSD- atrioventricular septal defect; CO-carbon monoxide; COA-coarctation of the aorta; d-TGA-d-transposition of the great arteries; HLHS-hypoplastic left heart syndrome; LVOTO-left ventricular outflow tract obstructions; NO_2-nitrogen dioxide; O_3-ozone; PM_{10}-particulate matter less than 10 microns in diameter; $PM_{2.5}$-particulate matter less than 2.5 microns in diameter; PVS-pulmonary valve stenosis; RVOTO-right ventricular outflow tract obstructions; SO_2-sulfur dioxide; TOF-tetralogy of Fallot; VSD_{pm}-perimembranous ventricular septal defects. Other conotruncal category includes common truncus, interrupted aortic-arch, type B and type not specified, double outlet right ventricle defects, and conoventricular septal defects. A double slash, '//' indicates truncation of the results. Squares indicate defect-groupings; circles indicate individual defects. Defect-groupings include all individual defects listed underneath with the following additions: LVOTO interrupted aortic arch-type A; APVR-total and partial APVR; RVOTO-Ebstein's Anomaly Those defects could not be analyzed within the hierarchical regression due to limited sample size. Loadings represent the relative weight of each of the original pollutant variables used to obtain the value of the computed factor. Odds ratios estimated from hierarchical regression models. First stage was a polytomous logistic model, adjusted for maternal race/ethnicity, age educational attainment, household income, maternal smoking status and alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio. Second stage was a linear model with indicator variables for defect, defect grouping and level of exposure. For all factors, the three categories of exposure are: 10^{th} centile to less than the 50^{th} centile (10-<50), 50^{th} centile to less than the 90^{th} centile (50-<90), at or greater than the 90^{th} centile (90+), with the referent level being less than the 10^{th} centile among controls. Pollutant levels which define the category cutpoints are provided in Table 2. See Supplemental Material, Table S5, for corresponding numeric data.

Figure 1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PM10
PM2.5
SO2
O3
LVOTO
Aortic Stenosis
COA
HLHS
Conotruncal
dTGA
TOF
Other Conotruncals
APVR
TAPVR
AVSD
RVOTO
Pulmonary/Tricuspid Atresia
PVS
Septal
VSDpm
ASD
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50–<90
90+
25–<50
50–<75
75+
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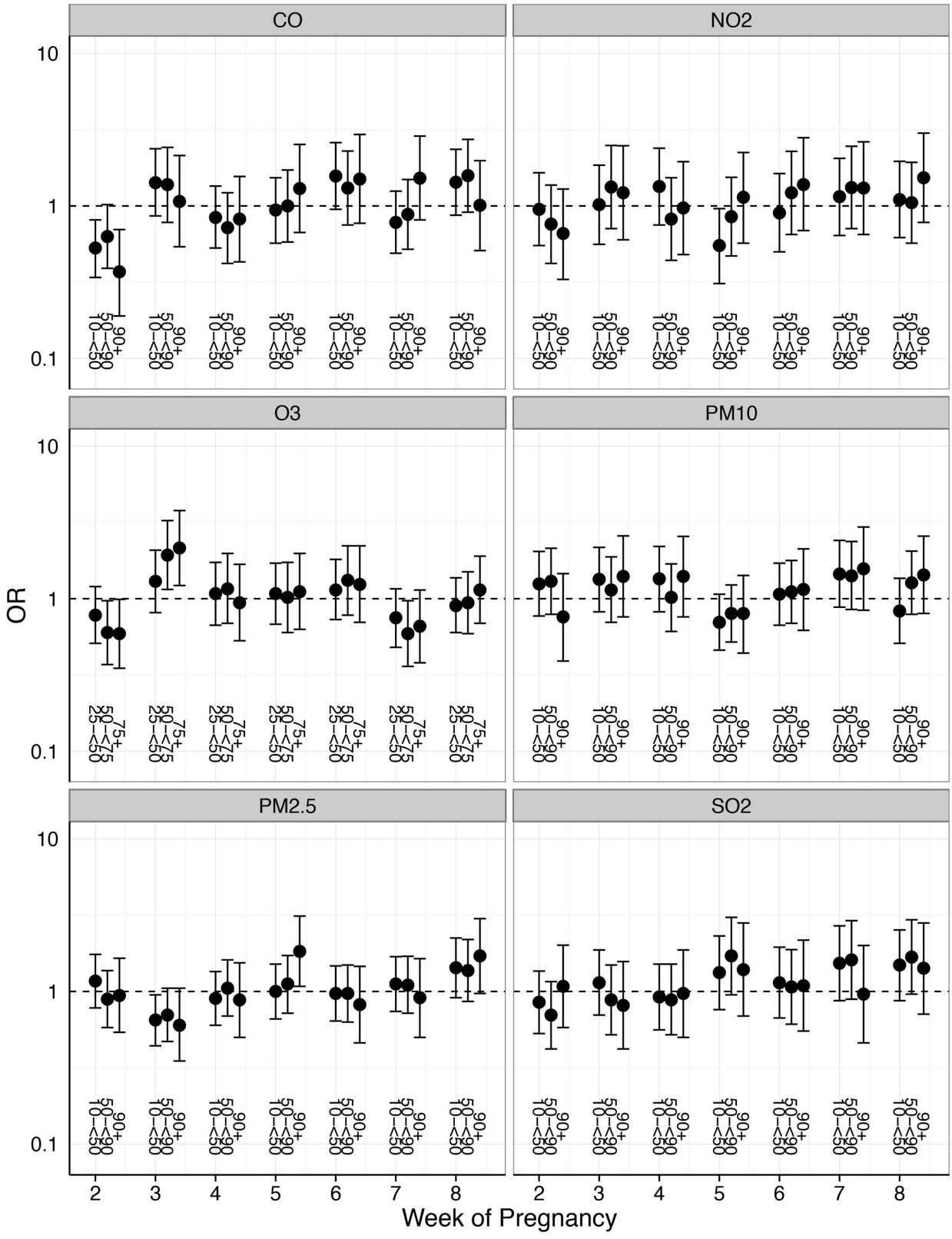
1
5

Figure 2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O3
PM10
PM2.5
SO2
OR
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1
0.1
10–<50
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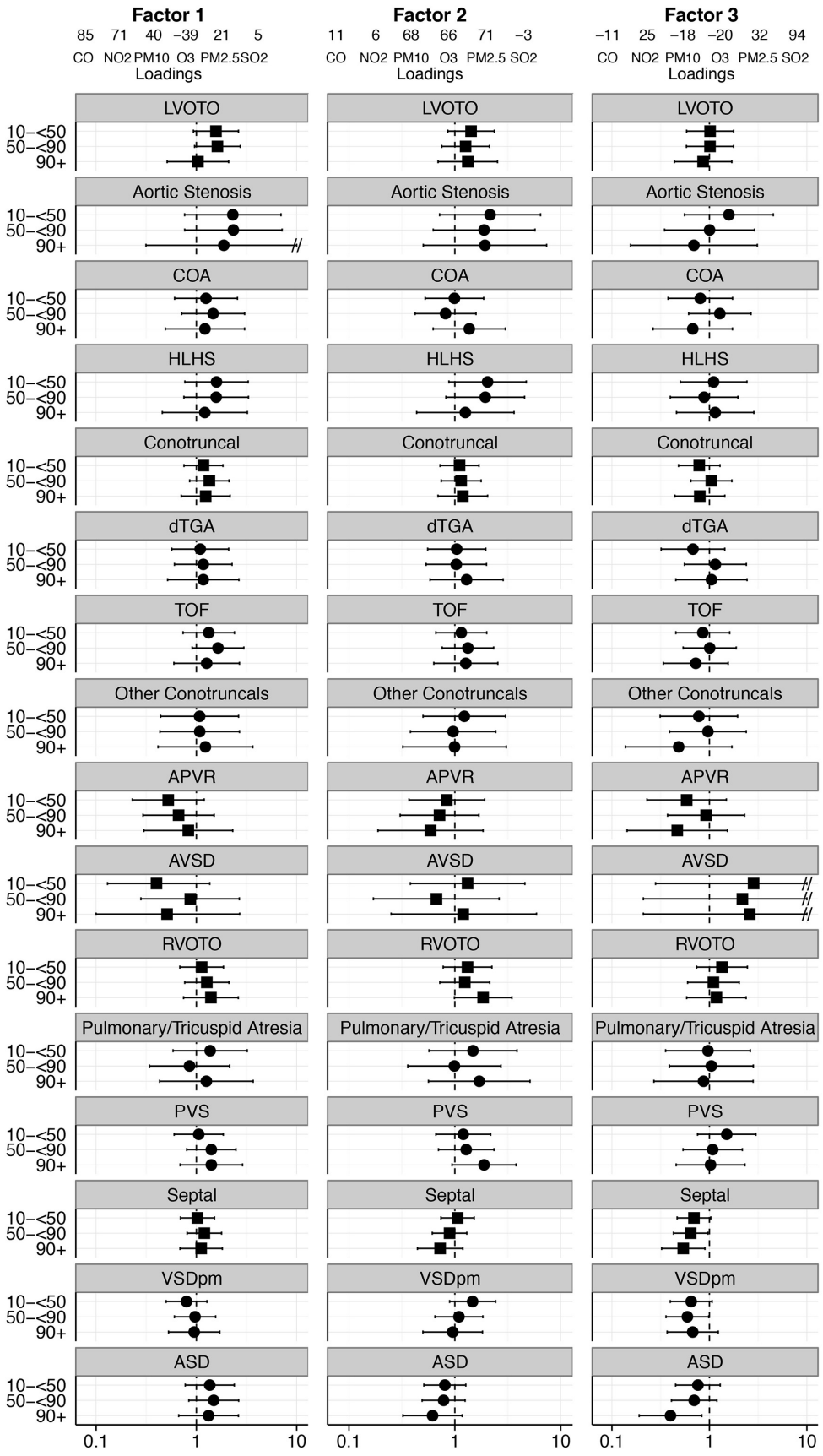
90+
25–<50
50–<75
75+
2
3
4
5
6
7
8
Week of Pregnancy

Figure 3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CO NO2 PM10 O3 PM2.5 SO2
Loadings
Factor 3
−11 25 −18 −20 32 94
CO NO2 PM10 O3 PM2.5 SO2
Loadings
LVOTO
Aortic Stenosis
COA
HLHS
Conotruncal
dTGA
TOF
Other Conotruncals
APVR
AVSD
RVOTO
Pulmonary/Tricuspid Atresia
PVS
Septal
VSDpm
ASD
10–<50
50–<90
90+
0.1
1
10